

COEURative

Creating Curative Strategies for
Cardiovascular Diseases
Associated with Cellular Hypoxia

John F. Schmedtje Jr., MD
President and CEO
Coeurative, Inc.

The proprietary compounds described in this presentation are protected under US Patents 10,501,471 and 10,913,748,
Nonprovisional US Patent Application 17,211,778, and International Patent Applications PCT/US19/58241 and PCT/US21/24540.
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Problem: Atherosclerotic Cardiovascular Disease

- ASCVD (atherosclerotic cardiovascular disease) will not disappear in our lifetimes.
- According to the American Heart Association Heart Disease and Stroke statistics, cardiovascular diseases in general (including coronary heart disease, heart failure, arterial disease, stroke, and hypertension)
 - are mostly secondary to ASCVD.
 - are found in 92 million Americans over the age of 20, or 36% of the adult population.
 - will lead to total annual US costs of \$1.1 Trillion in 2035.
 - cause 18 million deaths/year worldwide and will cause 22 million in 2030.
- There is no vaccine for ASCVD.
- We must improve upon the pharmaceutical options for treatment presently available.



The Disease: Hypoxia and inflammation are key factors in development of ASCVD

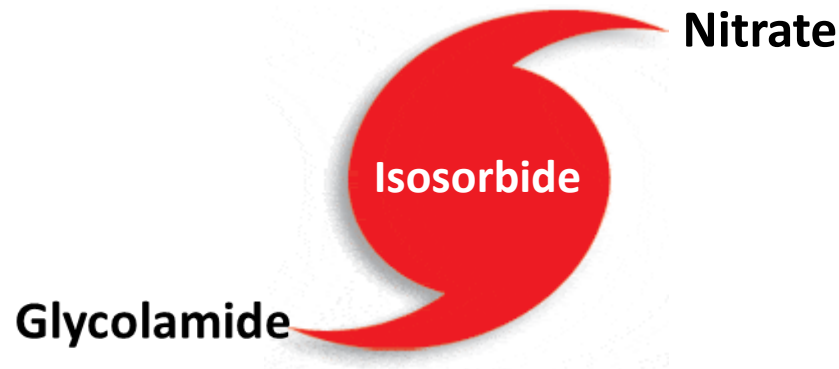
- Cardiac hypoxia leads to angina pectoris.
 - Nitric Oxide (NO) from oral NTG opens coronary arteries.
- Inflammation in the vascular endothelium is the first sign of ASCVD.
- Hypoxia and inflammation in heart diseases with very different etiologies may be reversed by the same molecule, NO.



- Nitric Oxide (NO) is donated by NTG (Nitroglycerin) to relax blood vessels quickly and briefly.
- Longer acting NO donors like isosorbide mononitrate are relatively weak.
- Targeted NO donors that reduce inflammation should provide a more long-lasting effect on ASCVD.

CR-0202 and CR-0305: Custom-Designed NO donors for ASCVD

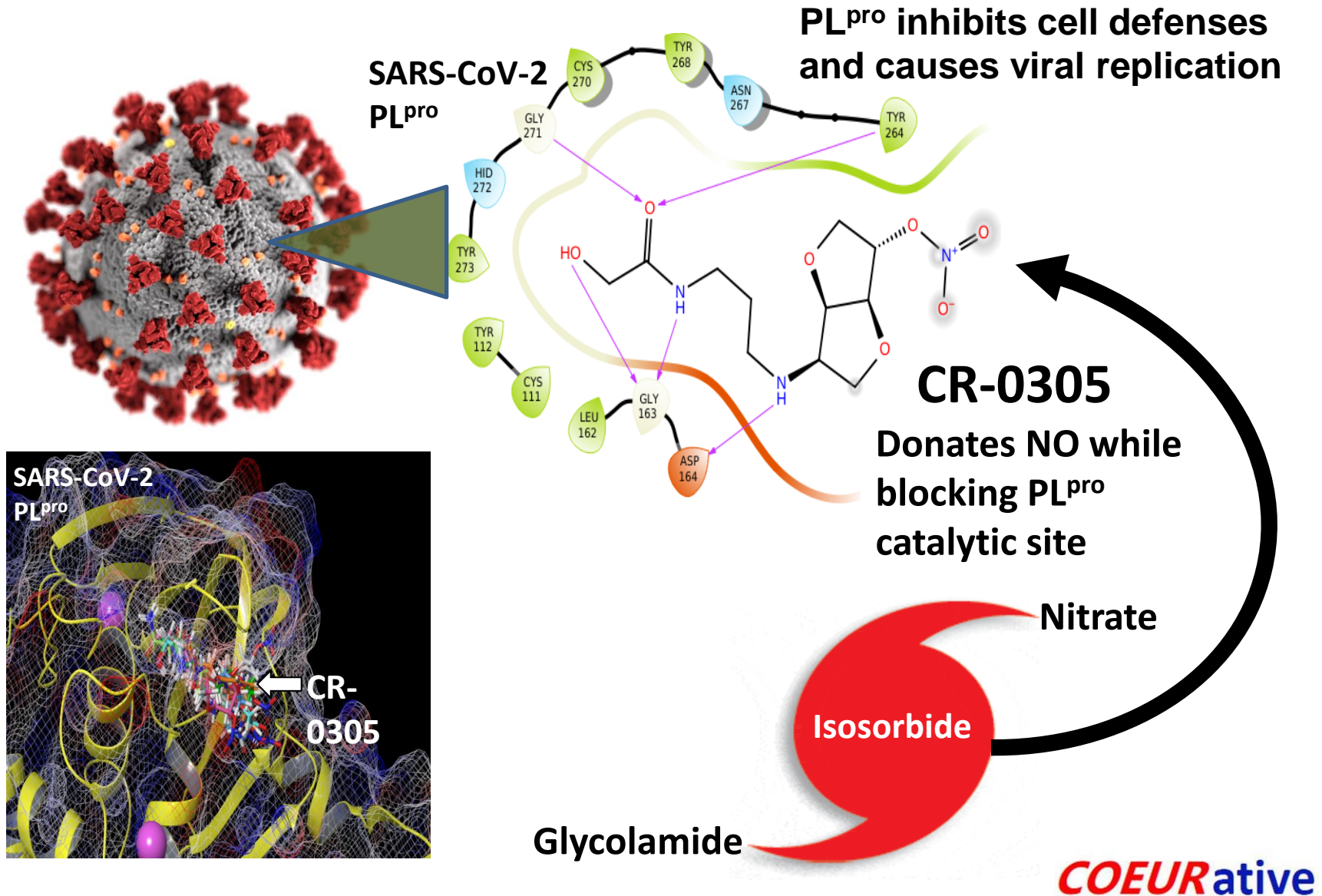
- Nitrate is an NO donor that dilates arteries and may protect against ischemia.
- Glycolamide is a urea analogue that can also facilitate NO formation.
- Targeted delivery of an oral agent that donates NO is desired for both ischemic preconditioning and to restore oxygenation.



CR-0202 and CR-0305 can deliver a “One-Two” punch:

- Nitrate group dilates vessels and reverses hypoxia
- Glycolamide optimizes NO production

CR-0202 and CR-0305 Are Also NO Donors and PL^{pro} Inhibitors for SARS-CoV-2 (virus of COVID-19)

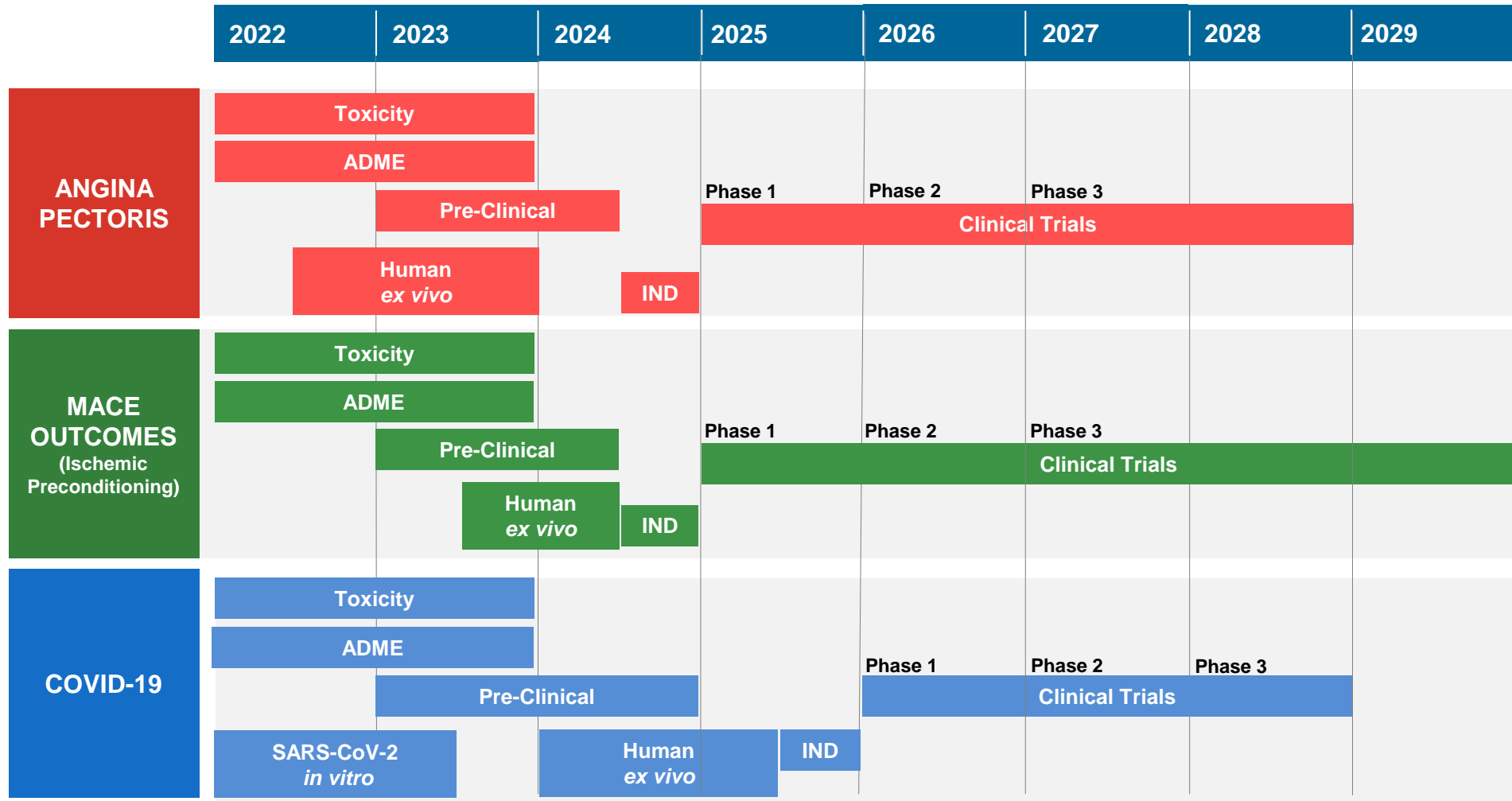


Milestones Achieved

- Company structure and dedicated lab facilities established.
- CR-0202 and CR-0305 synthesized for *in vitro* study.
- Patent no. 10,501,471 and 10,913,748 issued.
 - Nonprovisional US Patent Application 17,211,778 filed.
 - International Patent Applications PCT/US19/58241 and PCT/US21/24540 filed.
- “A Nitric Oxide Donor Binds to SARS-CoV-2 Papain-Like Protease with Therapeutic Implications” presented to American Heart Association.
 - Circulation, 2021; 144:A10067 OR https://doi.org/10.1161/circ.144.suppl_1.10067
- Toxicity tests passed *in vitro*. ADME experiments promising for oral use.
 - Human cell culture studies of mitochondrial function and ATP formation reveal little to no toxicity of CR-0202 and CR-0305 at five times expected peak human plasma concentration.
- Drug screening in mammalian cells infected by SARS-CoV-2 reveals that CR-0305 and CR-0202 reduced viral infection at a concentration near to that of known PL^{pro} inhibitor GRL-0617.
- Private investment to date: \$745,000.

Accelerated Development Plan

Contingent on Funding for Development of the Indications for CR-0202 and CR-0305



The Founder



- MD, 1981: Graduate of Honors Program in Medical Education at Northwestern University
- MPH, 1983: Harvard School of Public Health
- Internal Medicine Residency, 1986: Baylor College of Medicine
- Cardiology Fellow, 1991: Medical College of Virginia
- Faculty appointments at Baylor, University of Texas Medical Branch, Wake Forest University School of Medicine
- Published on hypoxia in medical science journals with high impact factors such as Circulation Research and Journal of Biological Chemistry
- Winner of the 1996 Cournand & Comroe Young Investigator Prize from the American Heart Association for cardiopulmonary research.
- Team player with a thirty-year track record of collaboration with the pharmaceutical industry on clinical trials and drug development.

COEURATIVE, Inc. is creating curative strategies for diseases associated with cellular hypoxia.



**201 McClanahan St SW, 2nd Floor
Roanoke, Virginia, USA
Email: jfs@coeurative.com**